Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended): A process of making a genetically engineered neisserial strain with an L2 or L3 LOS immunotype of reduced phase variability for manufacture of an immunogenic composition comprising the steps of:
a) selecting a neisserial strain with phase-variable LOS synthesis,
b) genetically engineering ~~said~~ the strain such that the homopolymeric nucleotide tract of a phase-variable lgtA and/or lgtG LOS oligosaccharide synthesis gene is modified to render the expression of ~~said~~ the gene less phase variable,
c) isolating L2 or L3 LOS from ~~said~~ the neisserial strain, and
d) formulating ~~said~~ the isolated L2 or L3 LOS with a pharmaceutically acceptable excipient.

2. (Currently amended): The process of claim 1, wherein the LOS oligosaccharide synthesis gene is modified to render the expression of ~~said~~ the gene non-phase variable.

3. (Currently amended): The process of claim 1 ~~or 2~~, ~~to make~~ ~~a~~ wherein the genetically engineered neisserial strain ~~with a~~ made has an LOS immunotype ~~which~~ that is non-phase variable.

4. (Currently amended): The process of claims 1~~-3~~, wherein the neisserial strain is selected from the group of a meningococcal strain and a meningococcus B strain~~, preferably meningococcus B~~.

5. (Currently amended): The process of claims 1~~-4~~, ~~to make~~ ~~a~~ wherein the genetically engineered neisserial strain ~~with an~~ made has L2 LOS immunotype.

6. (Previously presented): The process of claim 5, wherein step a) a neisserial strain with phase-variable L2 LOS synthesis is selected.

7. (Currently amended): The process of claim 5 ~~or 6~~, wherein step b) comprises the step of fixing ~~the~~ expression of ~~the~~ an IgtA gene product.

8. (Currently amended): The process of claim 7, wherein the expression of ~~the~~ an IgtA gene product is fixed by reducing the length of the homopolymeric nucleotide tract within the open-reading frame of the gene ~~whilst~~ and maintaining the open-reading frame in frame.

9. (Previously presented): The process of claim 8, wherein the homopolymeric G tract in the IgtA open-reading frame is reduced to 8, 5 or 2 consecutive G nucleotides.

10. (Currently amended): The process of claim~~s~~ 7 ~~9~~, wherein the expression of an IgtA gene product is fixed by changing the sequence of the homopolymeric G nucleotide tract within the open-reading frame of the IgtA gene such that: one or more GGG codons encoding Glycine is changed to any other codon encoding ~~g~~Glycine, or a codon encoding a conservative mutation, and/or the TCG codon encoding Serine is changed to any other codon encoding Serine, or a codon encoding a conservative mutation, ~~whilst~~ and maintaining the open-reading frame of the gene in frame.

11. (Currently amended): The process of claim 10, wherein 2, 3 or 4 codons in the homopolymeric tract are changed~~s, preferably to encode the identical amino acid~~ and encode the identical amino acid or a different amino acid.

12. (Currently amended): The process of claim~~s~~ 5 ~~11~~, wherein step b) comprises the step of fixing the expression of ~~the~~ an IgtG gene product.

13. (Currently amended): The process of claim 12, wherein the expression of ~~the~~ an IgtG gene product is fixed by reducing the length of the homopolymeric

nucleotide tract within the open-reading frame of the gene ~~whilst~~ and maintaining the open-reading frame in frame.

14. (Previously presented): The process of claim 13, wherein the homopolymeric C tract in the IgtG open-reading frame is reduced to 8, 5 or 2 consecutive C nucleotides.

15. (Currently amended): The process of claim~~s~~ 12~~-14~~, wherein the expression of an IgtG gene product is fixed by changing the sequence of the homopolymeric C nucleotide tract within the open-reading frame of the IgtG gene such that: one or more CCC codons encoding Proline is changed to any other codon encoding Proline, or a codon encoding a conservative mutation, ~~and/~~or the GCC codon encoding Alanine is changed to any other codon encoding Alanine, or a codon encoding a conservative mutation, ~~whilst~~ and maintaining the open-reading frame ~~of the gene~~ in frame.

16. (Currently amended): The process of claim 15, wherein 2, 3 or 4 codons in the homopolymeric tract are changed and encode the identical amino acid or a different amino acid~~, preferably to encode the identical amino acid~~.

17. (Currently amended): The process of claim 5~~ or 6~~, wherein step b) comprises the steps of (1) fixing the expression of ~~the~~ an IgtA gene product by reducing the length of the homopolymeric G nucleotide tract within the open-reading frame of the gene to 5 or 2 consecutive G nucleotides ~~whilst~~ and maintaining the open-reading frame ~~of the gene~~ in frame ~~(and~~ or optionally changing the sequence of the homopolymeric G nucleotide tract such that~~:~~ one or more GGG codons encoding Glycine is changed to any other codon encoding glycine, or a codon encoding a conservative mutation, ~~and/~~or the TCG codon encoding Serine is changed to any other codon encoding Serine, or a codon encoding a conservative mutation, ~~whilst~~ and maintaining the open-reading frame of the gene in frame~~)~~, and (2) fixing the expression of ~~the~~ an IgtG gene product by changing the sequence of the homopolymeric C nucleotide tract within the open-reading frame of the IgtG gene such that~~:~~ 1, 2 or 3 CCC codons encoding Proline is changed to any other codon

encoding Proline, or a codon encoding a conservative mutation, ~~and/~~or the GCC codon encoding Alanine is changed to any other codon encoding Alanine, or a codon encoding a conservative mutation, whilst maintaining the open-reading frame ~~of the gene~~ in frame.

18. (Currently amended): The process of claim~~s 1-4~~ 2, ~~to make a~~ wherein the genetically engineered neisserial strain ~~with~~ made has an L3 LOS immunotype.

19. (Previously presented): The process of claim 18, wherein step a) a neisserial strain with phase-variable L3 LOS synthesis is selected.

20. (Currently amended): The process of claim 18 or 19, wherein step b) comprises the step of fixing the expression of ~~the~~ an IgtA gene product.

21. (Currently amended): The process of claim 20, wherein the expression of the IgtA gene product is fixed by reducing the length of the homopolymeric nucleotide tract within the open-reading frame of the gene ~~whilst~~ and maintaining the open-reading frame in frame.

22. (Previously presented): The process of claim 21, wherein the homopolymeric G tract in the IgtA open-reading frame is reduced to 8, 5 or 2 consecutive G nucleotides.

23. (Currently amended): The process of claim~~s~~ 20~~-22~~, wherein the expression of an IgtA gene product is fixed by changing the sequence of the homopolymeric G nucleotide tract within the open-reading frame of the IgtA gene such that~~:~~ one or more GGG codons encoding Glycine is changed to any other codon encoding glycine, or a codon encoding a conservative mutation, ~~and/~~or the TCG codon encoding Serine is changed to any other codon encoding Serine, or a codon encoding a conservative mutation~~, whilst~~ and maintaining the open-reading frame of the gene in frame.

24. (Currently amended): The process of claim 23, wherein 2, 3 or 4 codons in the homopolymeric tract are changed and encode the identical amino acid or a different amino acid~~, preferably to encode the identical amino acid~~.

25. (Currently amended): The process of claim~~s~~ 18~~-24~~, wherein step b) comprises the step of permanently downregulating the expression of ~~functional~~ a gene product from the IgtG gene.

26. (Currently amended): The process of claim 25, wherein the expression of ~~functional~~ the gene product from the IgtG gene is switched off~~, preferably~~ optionally by deleting all or part of the promoter or open-reading frame of the gene.

27. (Currently amended): The process of claim 18~~ or 19~~, wherein step b) comprises the steps of fixing the expression of the IgtA gene product by reducing the length of the homopolymeric G nucleotide tract within the open-reading frame of the gene to 2 consecutive G nucleotides ~~whilst~~ and maintaining the open-reading frame ~~of the gene~~ in frame, and switching off the expression of ~~functional~~ gene product from the IgtG gene by deleting all or part of the promoter or open-reading frame of the gene.

28. (Currently amended): The process of claim~~s~~ 5~~-27~~, wherein step b) comprises the step of permanently downregulating the expression of ~~functional~~ gene product from the IgtC gene, ~~preferably~~ optionally by switching the gene off~~, most preferably~~ or by deleting all or part of the promoter or open-reading frame of the gene.

29. (Currently amended): The process of claim~~s~~ 5~~-28~~, wherein step a) comprises the step of selecting a neisserial strain that is IgtB, or step b) ~~additionally~~ comprises the step of genetically engineering ~~said~~ the strain such that the expression of ~~functional~~ gene product from the IgtB or IgtE gene is permanently downregulated, ~~preferably~~ optionally by switching the gene off~~, most preferably~~ or by deleting all or part of the promoter or open-reading frame~~ of the gene~~.

30. (Currently amended): The process of claims ~~5-29~~, wherein step a) comprises the step of selecting a neisserial strain that is unable to synthesise capsular polysaccharide, or step b) ~~additionally~~ comprises the step of genetically engineering ~~said~~ the strain such that it is unable to ~~synthesise~~ synthesize capsular polysaccharide~~,~~ ~~preferably~~ by permanently downregulating the expression of ~~functional~~ gene product from one of the following genes: saiD ~~(also known as synD)~~, ctrA, ctrB, ctrC, ctrD, synA ~~(equivalent to synX and siaA)~~, synB ~~(equivalent to siaB)~~ or synC ~~(equivalent to siaC), more preferably~~, optionally by switching the gene off~~, most preferably~~ or by deleting all or part of the promoter or open-reading frame ~~of the gene~~.

31. (Currently amended): The process of claims ~~5-30~~, wherein step a) comprises the step of selecting a neisserial strain that is msbB- ~~and/~~or htrB-, or step b) ~~additionally~~ comprises the step of genetically engineering ~~said~~ the strain such that the expression of functional gene product from the msbB ~~and/~~or htrB gene(s) is permanently downregulated, ~~preferably~~ optionally by switching the gene(s) off~~, most preferably~~ or by deleting all or part of the promoter or open-reading frame ~~of the gene(s)~~.

32. (Currently amended): A process of isolating L2 LOS comprising the steps of producing a genetically engineered neisserial strain with a fixed L2 immunotype by the process of claims ~~5-17, and~~ or 28-~~31~~; and isolating L2 LOS from the resulting strain.

33. (Currently amended): The process of claim 32, comprising the ~~additional~~ step of conjugating the L2 LOS to a carrier comprising a source of T-cell epitopes ~~and/~~or the step of presenting the L2 LOS in a liposome formulation.

34. (Currently amended): A process of isolating neisserial blebs having an L2 LOS immunotype, comprising the steps of producing a genetically engineered neisserial strain with a fixed L2 immunotype by the process of claims ~~5-17, and~~ or 28-~~31~~; and isolating blebs from the resulting strain.

35. (Currently amended): The process of claim 34, where the step of isolating blebs involves extraction with about 0.03%, ~~preferably~~ about 0.05-0.2%~~, most preferably around or exactly~~ or about or exactly 0.1% deoxycholate.

36. (Currently amended): The process of claim 34~~ and 35~~, comprising the ~~additional~~ step of intra-bleb conjugating the L2 LOS to an outer membrane protein ~~also~~ present in the blebs.

37. (Currently amended): A process of isolating L3 LOS comprising the steps of producing a genetically engineered neisserial strain with a fixed L3 immunotype by the process of claim~~s~~ 18~~-31~~; and isolating L3 LOS from the ~~resulting~~ strain.

38. (Currently amended): The process of claim 37, comprising the ~~additional~~ step of conjugating the L3 LOS to a carrier comprising a source of T-cell epitopes ~~and/~~or the step of presenting the L3 LOS in a liposome formulation.

39. (Currently amended): A process of isolating neisserial blebs having an L3 LOS immunotype, comprising the steps of producing a genetically engineered neisserial strain with a fixed L3 immunotype by the process of claim~~s~~ 18~~-31~~; and isolating blebs from the ~~resulting~~ strain.

40. (Currently amended): The process of claim 39, where the step of isolating blebs involves extraction with about 0.03%, ~~preferably~~ about 0.05-0.2%, ~~most preferably around or exactly~~ or about or exactly 0.1% deoxycholate.

41. (Currently amended): The process of claim 39~~ or 40~~, comprising the ~~additional~~ step of intra-bleb conjugating the L3 LOS to an outer membrane protein ~~also~~ present in the blebs.

42. (Currently amended): A process of making an immunogenic composition comprising the steps of producing isolated L2 LOS by the process of claim~~s~~ 32~~-33 or producing isolated neisserial blebs having an L2 LOS immunotype by the process of~~

~~claims 35-36,~~ and formulating ~~said~~ the L2 LOS ~~or blebs~~ with a pharmaceutically-acceptable excipient.

43. (Currently amended): A process of making an immunogenic composition comprising the steps of producing isolated L3 LOS by the process of claim~~s~~ 37~~-38 or producing isolated neisserial blebs having an L3 LOS immunotype by the process of claims 39-41,~~ and formulating ~~said~~ the L3 LOS ~~or blebs~~ with a pharmaceutically acceptable excipient.

44. (Currently amended): A process of making a multivalent immunogenic composition comprising the steps of producing isolated L2 LOS by the process of claim~~s~~ 32~~-33~~ or producing isolated neisserial blebs having an L2 LOS immunotype ~~by the process of claims 34-36~~, producing isolated L3 LOS ~~by the process of claims 37-38~~ or producing isolated neisserial blebs having an L3 LOS immunotype ~~by the process of claims 39-41,~~ and mixing ~~said~~ the L2 and L3 LOS components together along with a pharmaceutically acceptable excipient.

45. (Currently amended): A process of growing a high cell density of an L2 or L3 neisserial strain comprising the steps of:
a) genetically-engineering a neisserial strain according to claim~~s~~ 5~~-31~~;
b) growing the strain to high cell density in a fermentor.

46. (Currently amended): The process of claim 45, wherein the strain is grown to a cell density in iron non-limiting conditions of OD_{450} 10-19, or OD_{450} ~~preferably~~ 12-16~~, in iron non-limiting conditions,~~ or is grown to a cell density in iron limiting conditions of OD_{450} 6-12~~, preferably~~ or OD_{450} 8-10~~, in iron-limited conditions~~.

47. (Currently amended): A process of isolating neisserial L2 or L3 LOS comprising the steps of growing an L2 or L3 neisserial strain to high cell density according to the process of claim 45~~ or 46~~, and isolating L2 or L3 LOS from the resulting strain.

48. (Previously presented): The process of claim 47, comprising the ~~additional~~ step of conjugating the L2 or L3 LOS to a carrier comprising a source of T-cell epitopes ~~and/~~or the step of presenting the L2 or L3 LOS in a liposome formulation.

49. (Currently amended): A process of isolating neisserial blebs having an L2 or L3 LOS immunotype, comprising the steps of growing an L2 or L3 neisserial strain to high cell density according to the process of claim 45~~ or 46~~; and isolating blebs from the resulting strain.

50. (Currently amended): The process of claim 49, where the step of isolating blebs involves extraction with about 0-0.3%, about ~~preferably~~ 0.05-0.2%, ~~most preferably around or exactly~~ or about or exactly 0.1% deoxycholate.

51. (Currently amended): The process of claim 49~~ or 50~~, comprising the ~~additional~~ step of intra-bleb conjugating the L2 or L3 LOS to an outer membrane protein also present in the blebs.

52. (Currently amended): A process of making an immunogenic composition comprising the steps of producing isolated L2 or L3 LOS by the process of claim~~s~~ 47-~~48~~ or producing isolated neisserial blebs having an L2 or L3 LOS immunotype~~ by the process of claims 49-51,~~ and formulating ~~said~~ the L2 or L3 LOS or blebs with a pharmaceutically acceptable excipient.

53. (Currently amended): A process of making an immunogenic composition comprising the steps of producing isolated L2 LOS by the process of claim~~s~~ 47~~-48~~ or producing isolated neisserial blebs having an L2 LOS immunotype ~~by the process of claims 49-51~~, producing isolated L3 LOS~~ by the process of claims 47-48 or producing isolated neisserial blebs having an L3 LOS immunotype by the process of claims 49-51,~~ and mixing ~~said~~ the L2 and L3 LOS components together along with a pharmaceutically acceptable excipient.

54. (New): A process of making an immunogenic composition comprising the steps of producing isolated neisserial blebs having an L2 LOS immunotype by the process of claim 35, and formulating the L2 LOS or blebs with a pharmaceutically-acceptable excipient.

55. (New): A process of making an immunogenic composition comprising the steps of producing isolated L3 LOS by the process of claims 39, and formulating the L3 LOS or blebs with a pharmaceutically acceptable excipient.

56. (New): A process of making an immunogenic composition comprising the steps of producing isolated neisserial blebs having an L2 LOS immunotype by the process of claims 34, and mixing the L2 LOS or blebs with a pharmaceutically acceptable excipient.

57. (New): A process of making an immunogenic composition comprising the steps of producing isolated neisserial blebs having an L3 LOS immunotype by the process of claim 39, and mixing the L3 LOS or blebs with a pharmaceutically acceptable excipient.

58. (New): A process of making an immunogenic composition comprising the steps of producing isolated neisserial blebs having an L2 or L3 LOS immunotype by the process of claim 49, and formulating the L2 or L3 LOS or blebs with a pharmaceutically acceptable excipient.

59. (New): A process of making an immunogenic composition comprising the steps of producing isolated neisserial blebs having an L2 LOS immunotype by the process of claim 49, and mixing the L2 LOS or blebs and a pharmaceutically acceptable excipient.

60. (New): A process of making an immunogenic composition comprising the steps of producing isolated neisserial blebs having an L3 LOS immunotype by the process of claim 49, and mixing the L3 LOS or blebs with a pharmaceutically acceptable excipient.